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L4: Entry 77 of 77 File: USPT Nov 5, 1996

DOCUMENT-IDENTIFIER: US 5571675 A
TITLE: Detection and amplification of candiotrophin-1(cardiac hypertrophy factor)

Brief Summary Text (28):
In a still further aspect, the invention provides an isolated polypeptide encoded by a nucleic acid having a sequence that hybridizes under moderately stringent conditions to the nucleic acid sequence provided in FIG. 1. Preferably, this polypeptide is biologically active.

Brief Summary Text (30):
In a still further aspect, the invention provides a composition comprising biologically active CHF and a pharmaceutically acceptable carrier or comprising biologically active CHF fused to an immunogenic polypeptide.

Brief Summary Text (38):
The invention also provides an isolated DNA molecule having a sequence capable of hybridizing to the DNA sequence provided in FIG. 1 or FIG. 5 under moderately stringent conditions, wherein the DNA molecule encodes a biologically active CHF polypeptide, excluding rat CHF.

Detailed Description Text (6):
"CHF variants" or "CHF sequence variants" as defined herein mean biologically active CHFs as defined below having less than 100% sequence identity with the CHF isolated from recombinant cell culture or from murine embryoid bodies having the deduced sequence described in FIG. 1, or with the human equivalent described in FIG. 5. Ordinarily, a biologically active CHF variant will have an amino acid sequence having at least about 70% amino acid sequence identity with the CHF isolated from murine embryoid bodies or the mature human CHF (see FIGS. 1 and 5), preferably at least about 75%, more preferably at least about 80%, still more preferably at least about 85%, even more preferably at least about 90%, and most preferably at least about 95%.

Detailed Description Text (11):
"Biologically active" when used in conjunction with either "CHF" or "isolated CHF" mean a CHF polypeptide that exhibits hypertrophic, inotropic, anti-arrhythmic, or neurotrophic activity or shares an effector function of CHF isolated from murine embryoid bodies or produced in recombinant cell culture described herein, and that may (but need not) in addition possess an antigenic function. One principal effector function of CHF or CHF polypeptide herein is influencing cardiac growth or hypertrophy activity, as measured, e.g., by atrial natriuretic peptide (ANP) release or by the myocyte hypertrophy assay described herein using a specific plating medium and plating density, and preferably using crystal violet stain for readout. The desired function of a CHF (or CHF antagonist) is to increase physiological (beneficial) forms of hypertrophy and decrease pathological hypertrophy. In addition, the CHF herein is expected to display anti-arrhythmic function by promoting a more normal electrophysiological phenotype. Another principal effector function of CHF or CHF polypeptide herein is stimulating the proliferation of chick ciliary ganglion neurons in an assay for CNTF activity.

Detailed Description Text (14):
"Percent amino acid sequence identity" with respect to the CHF sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the CHF sequence isolated from murine embryoid bodies having the deduced amino acid sequence described in FIG. 1 or the deduced human CHF amino acid seqeunce described in FIG. 5, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. None of N-terminal, C-terminal, or internal extensions, deletions, or insertions into the CHF sequence shall be construed as affecting sequence identity or homology. Thus, exemplary biologically active CHF polypeptides considered to have identical sequences include prepro-CHF, pro-CHF, and mature CHF.

Detailed Description Text (16):
"Isolated CHF nucleic acid" is RNA or DNA containing greater than 16 and preferably 20 or more sequential nucleotide bases that encodes biologically active CHF or a fragment thereof, is complementary to the RNA or DNA, or hybridizes to the RNA or DNA and remains stably bound under moderate to stringent conditions. This RNA or DNA is free from at least one contaminating source nucleic acid with which it is normally associated in the natural source and preferably substantially free of any other mammalian RNA or DNA. The phrase "free from at least one contaminating source nucleic acid with which it is normally associated" includes the case where the nucleic acid is present in the source or natural cell but is in a different chromosomal location or is otherwise flanked by nucleic acid sequences not normally found in the source cell. An example of isolated CHF nucleic acid is RNA or DNA that encodes a biologically active CHF sharing at least 75%, more preferably at least 80%, still more preferably at least 85%, even more preferably 90%, and most preferably 95% sequence identity with the murine CHF or with the human CHF.

Detailed Description Text (56):
Optional preferred polypeptides of this invention are biologically active CHF variant(s) with an amino acid sequence having at least 70% amino acid sequence identity with the murine CHF of FIG. 1, preferably at least 75%, more preferably at least 80%, still more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95% (i.e., 70-100%, 75-100%, 80-100%, 85-100%, 90-100%, and 95-100% sequence identity, respectively). Alternatively, the preferred biologically active CHF variant(s) have an amino acid sequence having at least 70%, preferably at least 75%, more preferably at least 80%, still more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95% amino acid sequence identity with the human CHF sequence of FIG. 5 (i.e., 70-100%, 75-100%, 80-100%, 85-100%, 90-100%, and 95-100% sequence identity, respectively).

Detailed Description Text (61):
Other preferred naturally occurring biologically active CHF polypeptides of this invention include prepro-CHF, pro-CHF, pre-CHF, mature CHF, and glycosylation variants thereof.

Detailed Description Text (62):
Still other preferred polypeptides of this invention include CHF sequence variants and chimeric CHFs. Ordinarily, preferred CHF sequence variants are biologically active CHF variants that have an amino acid sequence having at least 70% amino acid sequence identity with the human or murine CHF, preferably at least 75%, more preferably at least 80%, still more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95%. An exemplary preferred CHF variant is a C-terminal domain CHF variant in which one or more of the basic or dibasic amino acid residue(s) (e.g., R or K) is substituted with a non-basic amino acid residue(s) (e.g., hydrophobic, neutral, acidic, aromatic, gly, pro and the like).

Detailed Description Text (69):
The invention also provides an isolated nucleic acid molecule encoding the CHF or fragments thereof, which nucleic acid molecule may be labeled or unlabeled with a detectable moiety, and a nucleic acid molecule having a sequence that is complementary to, or hybridizes under stringent or moderately stringent conditions with, a nucleic acid molecule having a sequence encoding a CHF. A preferred CHF nucleic acid is RNA or DNA that encodes a biologically active CHF sharing at least 75%, more preferably at least 80%, still more preferably at least 85%, even more preferably 90%, and most preferably 95%, sequence identity with the murine or human CHF.

Detailed Description Text (70):
More preferred isolated nucleic acid molecules are DNA sequences encoding biologically active CHF, selected from: (a) DNA based on the coding region of a mammalian CHF gene (e.g., DNA comprising the nucleotide sequence provided in FIG. 1 or FIG. 5, or fragments thereof); (b) DNA capable of hybridizing to a DNA of (a) under at least moderately stringent conditions; and (c) DNA that is degenerate to a DNA defined in (a) or (b) which results from degeneracy of the genetic code. It is contemplated that the novel CHFs described herein may be members of a family of ligands having suitable sequence identity that their DNA may hybridize with the DNA of FIG. 1 or FIG. 5 (or fragments thereof) under low to moderate stringency conditions. Thus, a further aspect of this invention includes DNA that hybridizes under low to moderate stringency conditions with DNA encoding the CHF polypeptides.

Detailed Description Text (92):
Other insertional variants of the native CHF molecule include the fusion to the N- or C-terminus of native CHF of immunogenic polypeptides, e.g., bacterial polypeptides such as beta-lactamase or an enzyme encoded by the E. coli trp locus, or yeast protein, and C-terminal fusions with proteins having a long half-life such as immunoglobulin constant regions (or other immunoglobulin regions), albumin, or ferritin, as described in WO 89/02922 published 6 Apr. 1989.

Detailed Description Text (143):
In addition, vectors derived from the 1.6 .mu.m circular plasmid pKD1 can be used for transformation of Kluyveromyces yeasts. Bianchi et al., Curr. Genet., 12: 185 (1987). More recently, an expression system for large-scale production of recombinant calf

chymosin was reported for K. lactis. Van den Berg, Bio/Technology, 8: 135 (1990). Stable multi-copy expression vectors for secretion of mature recombinant human serum albumin by industrial strains of Kluyveromyces have also been disclosed. Fleer et al., Bio/Technology, 9: 968-975 (1991).

Detailed Description Text (160):
Particularly useful in the practice of this invention are expression vectors that provide for the transient expression in mammalian cells of DNA encoding CHF. In general, transient expression involves the use of an expression vector that is able to replicate efficiently in a host cell, such that the host cell accumulates many copies of the expression vector and, in turn, synthesizes high levels of a desired polypeptide encoded by the expression vector. Sambrook et al., supra, pp. 16.17-16.22. Transient expression systems, comprising a suitable expression vector and a host cell, allow for the convenient positive identification of polypeptides encoded by cloned DNAs, as well as for the rapid screening of such polypeptides for desired biological or physiological properties. Thus, transient expression systems are particularly useful in the invention for purposes of identifying analogs and variants of native CHF that are biologically active CHF.

Detailed Description Text (186):
CHF variants in which residues have been deleted, inserted, or substituted are recovered in the same fashion as native CHF, taking account of any substantial changes in properties occasioned by the variation. For example, preparation of a CHF fusion with another protein or polypeptide, e.g., a bacterial or viral antigen, facilitates purification; an immunoaffinity column containing antibody to the antigen can be used to adsorb the fusion polypeptide. Immunoaffinity columns such as a rabbit polyclonal anti-CHF column can be employed to absorb the CHF variant by binding it to at least one remaining immune epitope. A protease inhibitor such as those defined above also may be useful to inhibit proteolytic degradation during purification, and antibiotics may be included to prevent the growth of adventitious contaminants. One skilled in the art will appreciate that purification methods suitable for native CHF may require modification to account for changes in the character of CHF or its variants upon production in recombinant cell culture.

Detailed Description Text (231):
Another method for assaying hypertrophy involves measuring for atrial natriuretic peptide (ANP) release by means of an assay that determines the competition for binding of .sup.125 I-rat ANP for a rat ANP receptor A-IgG fusion protein. The method suitable for use is similar to that used for determining gp120 using a CD4-IgG fusion protein described by Chamow et al., Biochemistry, 29: 9885-9891 (1990).

Detailed Description Text (286):
Alternatively, the phage display technology (McCafferty et al., Nature, 348: 552-553 [1990]) can be used to produce human antibodies and antibody fragments in vitro, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned inframe into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimicks some of the properties of the B-cell. Phage display can be performed in a variety of formats; for their review see, e.g., Johnson, Kevin S. and Chiswell, David J., Current Opinion in Structural Biology, 3: 564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson et al., Nature, 952: 624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol., 222: 581-597 (1991), or Griffith et al., EMBO J., 12: 725-734 (1993).

Detailed Description Text (287):
In a natural immune response, antibody genes accumulate mutations at a high rate (somatic hypermutation). Some of the changes introduced will confer higher affinity, and B cells displaying high-affinity surface immunoglobulin are preferentially replicated and differentiated during subsequent antigen challenge. This natural process can be mimicked by employing the technique known as "chain shuffling" (Marks et al., Bio/Technol., 10: 779-783 [1992]). In this method, the affinity of "primary" human antibodies obtained by phage display can be improved by sequentially replacing the heavy and light chain V region genes with repertoires of naturally occurring variants (repertoires) of V domain genes obtained from unimmunized donors. This technique allows the production of antibodies and antibody fragments with affinities in the nM range. A strategy for making very large phage antibody repertoires has been described by Waterhouse et al., Nucl. Acids Res., 21: 2265-2266 (1993).

Detailed Description Text (288):
Gene shuffling can also be used to derive human antibodies from rodent antibodies, where the human antibody has similar affinities and specificities to the starting rodent antibody. According to this method, which is also referred to as "epitope imprinting", the heavy or light chain V domain gene of rodent antibodies obtained by phage display technique is replaced with a repertoire of human V domain genes, creating rodent-human chimeras. Selection on antigen results in isolation of human

variable capable of restoring a functional antigen-binding site, i.e. the epitope governs (imprints) the choice of partner. When the process is repeated in order to replace the remaining rodent V domain, a human antibody is obtained (see PCT WO 93/06213, published 1 Apr. 1993). Unlike traditional humanization of rodent antibodies by CDR grafting, this technique provides completely human antibodies, which have no framework or CDR residues of rodent origin.

Detailed Description Text (336):
These assays were also positive for a second measure of cardiac hypertrophy-ANP release. See FIG. 3. This assay was performed by determination of the competition for the binding of .sup.125 I-rat ANP for a rat ANP receptor A-IgG fusion protein. This method is similar to that used for the determination of gp120 using a CD4-IgG fusion protein (Chamow et al., Biochemistry, 29: 9885-9891 [1990]). Briefly, microtiter wells were coated with 100 .mu.L of rat anti-human IgG antibody (2 .mu.g/mL) overnight at 4.degree. C. After washing with phosphate-buffered saline containing 0.5% bovine serum albumin, the wells were incubated with 100 .mu.L of 3 ng/mL rat ANP receptor A-IgG (produced and purified in a manner analogous to the human ANP receptor A-IgG (Bennett et al., J. Biol. Chem., 266: 23060-23067 [1991]) for one hour at 24.degree. C. The wells were washed and incubated with 50 .mu.L of rat ANP standard or sample for one hour at 24.degree. C. Then 50 .mu.L of .sup.125 I-rat ANP (Amersham) was added for an additional one-hour incubation. The wells were washed and counted to determine the extent of binding competition. ANP concentrations in the samples were determined by comparison to a rat ANP standard curve.

Detailed Description Text (430):
To show that human CT-1 encoded by clone h5 is biologically active, the EcoRI fragment was cloned into the mammalian expression vector pRK5 (EP 307,247) at the unique EcoRI site to give the plasmid pRK5.hu. CT1. This plasmid was transfected into human 293 cells, and the cells were maintained in serum-free medium for 3-4 days. This medium was then assayed for cardiac myocyte hypertrophy as described above for mouse CHF. The transfected 293 conditioned medium was clearly active in this assay (hypertrophy score of 5.5 at a dilution of 1:20).

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The Contents of Case 09764918

Qnum	Query	DB Name	Thesaurus	Operator	Plural
Q1	2001WO-US12013!	DWPI	ASSIGNEE	ADJ	YES
Q2	serum albumin	USPT	ASSIGNEE	ADJ	YES
Q3	Q2 and stab$5	USPT	ASSIGNEE	ADJ	YES
Q4	chimeric or heterologouls	USPT	ASSIGNEE	ADJ	YES
Q5	Q4 and half life	USPT	ASSIGNEE	ADJ	YES
Q6	Q5 and Q4 and Q3	USPT	ASSIGNEE	ADJ	YES
Q7	increase half life	USPT	ASSIGNEE	ADJ	YES
Q8	Q7 and Q6	USPT	ASSIGNEE	ADJ	YES
Q9	Q8 and chimeric polypeptide comprising serum albumin	USPT	ASSIGNEE	ADJ	YES
Q10	Q8 and human serum albumin	USPT	ASSIGNEE	ADJ	YES
Q11	5766883.pn.	USPT	ASSIGNEE	ADJ	YES

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L10	L9 and cystein loop	0	L10
L9	L8 and cyst$4	392	L9
L8	L7 and insert$2	591	L8
L7	L6 and loop	783	L7
L6	human serum albumin	6204	L6
L5	L2 and cysteine loop	11	L5
L4	L3 and loop	2180	L4
L3	L2 and cys$4	9160	L3
L2	serum albumin	31751	L2
DB=USPT; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L1	serum albumin	29634	L1